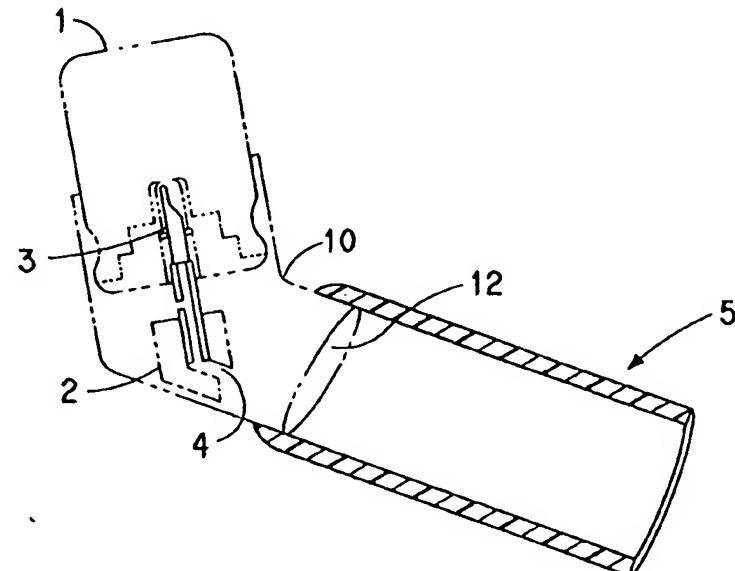


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<p>(54) Title: BUILD-UP RESISTANT SPACERS FOR METERED DOSE INHALERS</p> <p>(57) Abstract</p> <p>A spacer (5) for a metered dose inhaler (1) is provided which resists build-up of the dispensed drug from the inhaler by having the interior surface of the spacer comprise fluoropolymer (24).</p> 		

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TITLE**BUILD-UP RESISTANT SPACERS FOR
METERED DOSE INHALERS****RELATED APPLICATION**

5 This application claims the benefit of provisional application Serial No. 60/030,152, filed November 1, 1996.

FIELD OF THE INVENTION

 The instant invention relates to a new spacer design for metered dose inhalers by using effective amounts of a suitable fluoropolymer which prevents
10 build-up of the drug on the inside walls of the spacer and improves delivery to patients.

BACKGROUND OF THE INVENTION

 Spacers are attachments used with metered dose inhalers (MDIs) primarily to maximize transport of a drug into the respiratory airways and minimize
15 oropharyngeal deposition. These attachments are typically made of a plastic material such as polycarbonate or polystyrene and are available in many different designs having an annular cross-section and being open at each end, such designs including hollow cylinder and hollow cone . The spacer is attached to the metered dose inhaler in a way that the spacer receives the metered dose of the drug. The
20 patient using the inhaler then inhales the drug from the interior of the spacer.

 While spacers are effective in improving the depth of drug penetration, thereby minimizing the amount of esophageal impaction (and, therefore, product swallowing) and increasing the total amount of drug deposited in the lungs, the primary disadvantage of a spacer is the potential build-up of the drug (active
25 ingredient possibly accompanied by other ingredients present in the drug, e.g. carriers, surfactant) that can occur within the spacer. Build-up can occur for several reasons, but the most predominant is electrostatic activity. The consequences of drug build up in the spacer include a higher possibility of microbial growth within the spacer, increased difficulty cleaning the spacer and
30 premature disposal of the metered dose inhaler, among others.

SUMMARY OF THE INVENTION

The present invention solves problems associated with the use of a spacer attached to a metered dose inhaler by reducing the undesired build-up of the drug dispensed by the inhaler. The solution provided by the present invention relates to
5 the development of spacers for metered dose inhalers that are resistant to build-up of the drug (active ingredients) upon the inside wall (interior surface) of the spacer.

It has been found that when the interior surface of the spacer is comprised of fluoropolymer, the drug does not build up on such surface, whereby the patient
10 inhaling the drug receives the full metered dose of the drug and the other problems associated with drug build-up do not arise.

Build-up resistance by the spacer of the present invention can be achieved by a number of different ways of obtaining the fluoropolymer interior surface, such as by (1) coating the interior surface with fluoropolymer, (2) applying a
15 fluoropolymer lining to the interior surface by using an adhesive, or (3) manufacturing the spacer entirely out of a fluoropolymer.

Preferably, method (1) is used for reasons of economics, in that the structural integrity of the spacer can be obtained by the spacer being first made of conventional plastics (for that purpose), which are less expensive than
20 fluoropolymer, and using the more expensive fluoropolymer as a relatively thin coating only for rendering the interior surface of the spacer non-attractive to the dispensed drug.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows schematically and side view cross-section a portion of a
25 metered dose inhaler incorporating a spacer of the present invention. The metered dose inhaler is shown in phantom lines.

Fig. 2 shows schematically and in side view cross-sectional enlargement another embodiment of a spacer of annular design of the present invention.

DETAILED DESCRIPTION

30 The present invention relates to the development of a build-up resistant spacer for use in delivering medicaments by any metered dose inhaler (MDI). MDIs are used to deliver dermal, pulmonary or mucosal (e.g., buccal or nasal)

administration of such drugs as antiallergic agents, analgesics, bronchodilators, antihistamines, antitussives, antianginal agent, antibiotics, anti-inflammatory agents, hormones, peptides, steroids, enzymes, sulphonamides, among others. A typical metered dose inhaler is illustrated in Fig. 1. In Fig. 1, the MDI comprises an aerosol container 1 which holds the active ingredient (drug) to be delivered and a propellant such as 1,1,1,2-tetrafluoroethane (HFC-134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea) or one of the older propellants such as CFC 11, 12, or 114. The MDI also has an outer sleeve 10 which is slidably mounted on the exterior of the container 1, and the sleeve 10 has an outlet spout 12. Other components of the MDI include an actuator 2, a metering valve 3, a means defining an actuator orifice 4 which faces the spout 12, and a spacer 5 slip fit over the exterior of the spout. The actuator 2 and metering valve 3 operate conventionally upon application of external force on the sleeve 10 to cause it to slide along (into) the container 1 to operate the actuator 2 to deliver a metered dose amount of the drug through the orifice 4 into the interior of the spacer 5 via spout 12, from which the dispensed drug can then be inhaled. The drug may be dissolved or dispersed in the propellant, and at least in the latter case, would be in the form of a powder as dispensed by the aerosol container into the spacer.

The dimensions of spacer 5 can be tailored to control the delivery pattern of the medicament to improve the depth of drug penetration, minimize the amount of esophageal impaction (and, therefore, product swallowing) and increase the total amount of drug deposited into the lungs. Typically, the spacer will have an annular cross-sectional such as a hollow cylinder which has an outlet having a shape which can be tolerated by the mouth of the patient. In the case of the spacer being a hollow cylinder, dimensions of the cylinder will generally fall within a cylinder length of 50 to 300 mm millimeters and an inner diameter of 24 to 40 mm. More often the cylinder length and inner diameter dimensions will be from 50-100 mm and 24 to 32 mm, respectively. Similar spacer lengths will be used when the spacer has a different design. In the case of the spacer having the design of hollow cones connected together at their bases, to provide an expansive interior volume, the largest interior diameter of the spacer (at the base of the cones), can be e.g. 100 to 150 mm.

The effectiveness of the MDI is improved by employing one or more of the previously identified fluoropolymer embodiments. In the embodiment of Fig. 1, the entire spacer is made of fluoropolymer. In the embodiment of Fig. 2, wherein the spacer 20 of cylindrical design is shown to comprise an outer layer 22 and an inner layer 24, the outer layer forms the structural component of the spacer, of such plastic as polycarbonate or polystyrene, and the inner layer 24 comprises fluoropolymer. The fluoropolymer is preferably coated onto the inner surface of the cylinder of plastic, and the coating can be very thin depending on the fluoropolymer used and the method of application. For example, fluoropolymers which are soluble in solvents which do not dissolve the plastic cylinder can form coatings as thin as 0.5 to 5 micrometers, as compared to the thickness of the plastic making up the outer layer of the spacer, which will be on the order of 1 to 5 mm. The spacer 20 has openings at opposite ends, opening 26 being the inlet for the dispensed drug and opening 28 being the outlet into the mouth of the patient.

The fluoropolymer will generally comprises at least 35 wt% fluorine. Examples of fluoropolymers include polytetrafluoroethylene (PTFE), melt-fabricable tetrafluoroethylene copolymers such as fluorinated ethylene-propylene (FEP), perfluoroalkoxy polymer (PFA), also known as copolymer of tetrafluoroethylene and perfluoro(alkyl vinyl ether) wherein the alkyl group contains 1 to 6 carbon atoms, preferably 2 or 3 carbon atoms, ethylene-tetrafluoroethylene copolymer (ETFE) polyvinylidene fluoride (PVDF), ethylene-chlorotrifluoroethylene copolymer (ECTFE), mixtures thereof, among others (some of these fluoropolymers are sold by the DuPont Company, Wilmington, Delaware under the trademark TEFLON®). As is well known, small amounts of additional comonomer can be present to improve properties of the copolymer. Additional examples of fluoropolymers are copolymers of perfluoro-2,2-dimethyl-1,3-dioxole with comonomer such as tetrafluoroethylene or chlorotrifluoroethylene such as disclosed in U.S. Patent 4,754,009 and copolymers of tetrafluoroethylene with a sufficient amount of other monomer than the resultant copolymer has increased solubility and is preferably even amorphous. Examples of such copolymers include partially crystalline copolymers of

tetrafluoroethylene with hexafluoropropylene (HFP) wherein the HFP content is characterized by an HFPI of 6.4 to 9 as disclosed in U.S. Patent 5,266,639, and amorphous copolymers wherein the HFP content is even higher, e.g. at least 20 mol% as disclosed in U.S. Patents 5,543,217 and 5,478,905.

5 Preferably the spacer is transparent, so that the user of the MDI can see the cleanliness and lack of drug buildup on the interior surface of the spacer. The fluoropolymer can be transparent in thick sections, e.g. the thickness of the cylinder wall forming the spacer when the fluoropolymer is amorphous. Even partially crystalline fluoropolymers will be sufficiently transparent when used as
10 very thin coatings on the interior surface of a cylinder of transparent plastic, e.g. polycarbonate or polystyrene.

Thin films of fluoropolymer can be adhered to the outer layer of plastic forming the structural portion of the spacer to form a coating of fluoropolymer on the interior surface of the spacer by first etching the film with sodium naphthalene
15 and then using an epoxy adhesive to adhere the etched surface of the film to the spacer interior surface.

Alternatively, the fluoropolymer coating can be applied to the interior surface of the plastic cylinder by coating the interior surface with a solution of fluoropolymer. Examples of solvents include perfluorooctane, perfluoro(2-butyl
20 tetrahydrofuran), and perfluorinated cycloalkane as disclosed in U. S. Patent 5,459,191. The fluoropolymer is selected so that it has solubility in the solvent. After application of the solution to the interior surface, the coating is dried to remove the solvent, leaving a fluoropolymer coating on the surface.

Another method for coating the interior surface with fluoropolymer
25 involves plasma deposition, wherein the surface is exposed to a plasma in the presence of fluoromonomer vapor, to cause the deposition of the vapor on the surface where the fluoromonomer polymerizes to form the coating. For example, the coating can be formed using hexafluoropropylene as the vaporized fluoromonomer and RF discharge operating at 100 watts, 50 mTorr and 5 min.
30 exposure.

Fluoropolymers tend not to attract the spray of drug entering the spacer from the MDI and therefor tend to avoid buildup of any of the drug on the interior

surface of the spacer when the interior surface comprises fluoropolymer. This lack of buildup is believed to come from the spray of drug and the fluoropolymer spacer interior surface both being negatively electrically charged. To insure that opposite electrostatic charge between the sprayed drug and the interior surface of the spacer does not arise, the fluoropolymer forming the interior surface can also contain electrically conductive carbon particles sufficient to dissipate any opposite electrical charge while not destroying transparency.

Examples

The inside walls of a plastic spacer for a metered dose inhaler are coated with polytetrafluoroethylene (PTFE) or other fluoropolymer polymer or copolymer including, but not limited to FEP, ETFE, or PFA. by spraying, dipping, brushing or any suitable application method. This creates a nonstick surface onto which the pharmaceutical agents and other components of the formulated drug product will not adhere or accumulate.

Two commercially available spacers in cylindrical form believed to made of polycarbonate are tested for drug buildup as follows:

Allen & Hansburys Volumatic® - 23 cm long and 9 cm double cone annular design; inlet and outlet openings of about 25 mm

Forest Pharmaceuticals Aerochamber® - 15 cm long and 4.5 cm in inner diameter

The interior surfaces of both spacers are partially coated with fluoropolymer solution (one wt% fluoropolymer) and dried, with the resultant fluoropolymer coating being visible so as to be distinguishable from the uncoated portion. The fluoropolymer is tetrafluoroethylene/hexafluoropropylene copolymer having a weight average molecular weight of 450,000 and containing 50 wt% of each monomer, and the solvent is perfluorooctane. The fluoropolymer is made essentially by the process of Examples 15 and 17 of U.S. Patent 5,478,905. An MDI containing a drug/propellant mixture is sprayed for 5 seconds into each spacer. It is observed that drug buildup occurs on the uncoated areas of the interior surface of the spacers, while no buildup is observed on the coated area. This test is repeated except that the contents of the MDI are sprayed directly on the interior surface instead of aiming through the spacer so that buildup occurs on

both coated and uncoated areas. The buildup is allowed to dry and then the spacer is subjected to rinsing in water. The buildup on the coated area washes away in 15 seconds, while the buildup on the uncoated area requires 40 seconds of rinsing to wash away the buildup.

- 5 Spacers like the two spacers described above are cleaned by rinsing in acetone and drying and then tested for adhesion of the fluoropolymer coating when applied by soaking in a solution rather than by a spray. The same fluoropolymer as described above is used except that the solution is 3 wt% of the fluoropolymer. A primer solution of 3 wt%
- 10 tetrafluoroethylene/hexafluoropropylene/maleic anhydride copolymer in acetone is prepared. In one series of experiments, just the fluoropolymer/perfluorooctane solution is used, and the coating is carried out as follows: One end of each of the two different spacers is closed by pressing against a smooth sheet of polyethylene. Each spacer is then filled with the fluoropolymer solution. After waiting one
- 15 minute, the spacers are drained, air dried for one hour and then oven dried at 50°C for 4 hours. The resultant fluoropolymer coating rinses well to discharge any buildup of drug, but is subject to removal from the interior surface of the spacer by scratching with a fingernail. Repetition of this experiment using clean spacers and application of the primer to the interior surface by the same procedure as the
- 20 fluoropolymer solution is applied, followed by application of the fluoropolymer solution in perfluorooctane to the dried primer layer, whereby the primer forms an intermediate layer, gives a layer that both resists drug buildup and removal by scratching with a fingernail. The composite layer is also not removed by rubbing with a No. 101 eraser from Eberhard Faber. Thus the composite fluoropolymer
- 25 coating can be cleaned by scrubbing as well as by rinsing if the need arises.

- The tetrafluoroethylene/hexafluoropropylene/maleic anhydride copolymer is made by the following procedure: A mixture of 2000 g of hexafluoropropylene, 110 g of tetrafluoroethylene and 5 g of maleic anhydride dissolved in 10 ml of trifluoroacetic acid, and 1.1 g of nitrogen trifluoride is made in a one gallon
- 30 reservoir. About 1120 g of this mixture are added to a polymerization autoclave which is shaken and heated at 250°C for 125 min. The contents of the autoclave are then removed and dried under vacuum, yielding 80 g of yellow colored

polymer, which analyzes as follows: wt. average molecular weight of 88,600, 61.4 mol% of TFE (carbon-13 NMR), 37.7 mol% HFP (carbon-13NMR) and 0.9 mol% maleic anhydride (carbon-13 NMR in hexafluorobenzene at 60°C, absorption @ 161ppm).

5 Similar results on buildup resistance are obtained when the fluoropolymer coating on the interior surface of the spacer is a fluoropolymer film laminated to the surface and when the entire spacer is made of fluoropolymer.

 A formulation of fluoropolymer along with an electrically conductive material is applied to the inside of an MDI spacer. The conductive material
10 eliminates the buildup of static electricity during the ingestion of the medication, thereby eliminating the resultant loss of active ingredient (powder) by either random powder repulsion or by electrostatic adhesion of the powder on the MDI spacer. The electrically conductive material is in the form of carbon, or other anti-static material.

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THE FOLLOWING IS CLAIMED:

1. A process comprising coating the interior surface of a spacer for use with a metered dose inhaler with fluoropolymer, the coating optionally containing an anti-static electrically conductive material.
- 5 2. A spacer for use with a metered dose inhaler, the interior surface of said spacer comprising fluoropolymer, optionally containing antistatic material.
3. The spacer of claim 2 wherein the spacer is made of said fluoropolymer.
4. The spacer of claim 2 wherein the spacer comprises an outer layer of plastic and an inner layer forming said interior surface of said fluoropolymer.
- 10 5. The spacer of claim 4 wherein said fluoropolymer is tetrafluoroethylene/hexafluoropropylene copolymer.
6. The spacer of claim 2 which is transparent.
7. The spacer of claim 4 wherein said inner layer is adhered to said outer layer through an intermediate layer of primer.
- 15

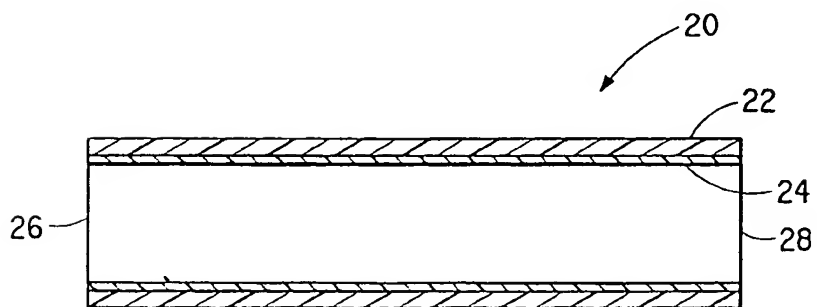
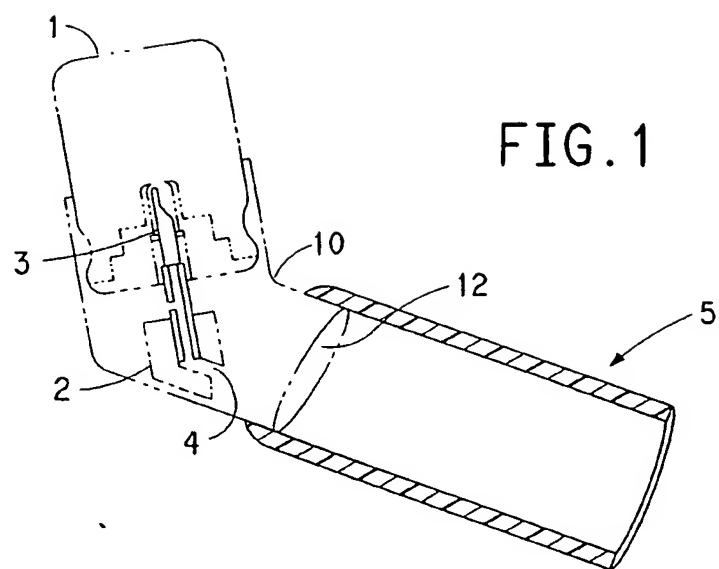


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19681

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, GPIC

search terms: mdi, inhaler#, static, antistatic, coatings, sprays, teflon, ptfe, polytetrafluoroethylen, fluoropolymers, cloud chamber, spacer, expansion chamber